ORIGINAL ARTICLE

Treatment expectations and perception of therapy in adult patients with spinal muscular atrophy receiving nusinersen

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Abstract

Background and purpose: This was an investigation of treatment expectations and of the perception of therapy in adult patients with 5q-associated spinal muscular atrophy (5q-SMA) receiving nusinersen.

Methods: A prospective, non-interventional observational study of nusinersen treatment in adult 5q-SMA patients was conducted at nine SMA centers in Germany. The functional status, treatment expectations and perceived outcomes were assessed using the Amyotrophic Lateral Sclerosis Functional Rating Scale—extended (ALS-FRS-ex), the Measure Yourself Medical Outcome Profile (MYMOP2), the Treatment Satisfaction Questionnaire for Medication (TSQM-9) and the Net Promoter Score (NPS).

Thomas Meyer and André Maier contributed equally.

Results: In all, 151 patients were included with a median age of 36 years (15–69 years). SMA type 3 (n = 90, 59.6%) prevailed, followed by type 2 (33.8%) and type 1 (6.6%). In SMA types 1–3, median ALS-FRS-ex scores were 25, 33 and 46 (of 60 scale points), respectively. MYMOP2 identified distinct treatment expectations: head verticalization (n = 13), bulbar function (n = 16), arm function (n = 65), respiration (n = 15), trunk function (n = 34), leg function (n = 76) and generalized symptoms (n = 77). Median symptom severity decreased during nusinersen treatment (median observational period 6.1 months, 0.5–16 months) from 3.7 to 3.3 MYMOP2 score points (p < 0.001). The convenience of drug administration was critical (49.7 of 100 TSQM-9 points, SD 22); however, the overall treatment satisfaction was high (74.3, SD 18) and the recommendation rating very positive (NPS +66).

Conclusions: Nusinersen was administered across a broad range of ages, disease durations and motor function deficits. Treatment expectations were highly differentiated and related to SMA type and functional status. Patient-reported outcomes demonstrated a positive perception of nusinersen therapy in adult patients with 5q-SMA.

INTRODUCTION

Spinal muscular atrophy (SMA) is a rare neurodegenerative disorder of motor neurons in the spinal cord and brain stem leading to progressive paresis and muscle atrophy of the extremities, the trunk and bulbar region. The loss of motor function translates into a decline in patient mobility, communication abilities, autonomy and social inclusion. The involvement of respiratory muscles may result in hypoventilation and the need for non-invasive or mechanical ventilation. However, the time of onset, progression rate and disease severity are highly variable and clinically classified in distinct SMA types [1–4].

In the majority of SMA patients the disease is caused by mutations or deletions in the SMN1 gene on chromosome 5q (5q-SMA), leading to reduced expression of the SMN protein [5]. In 2017, nusinersen was approved for the treatment of 5q-SMA in the European Union. The drug modifies splicing of SMN2-pre-mRNA, thus producing an enhanced expression of functional SMN protein. The approval of nusinersen was based primarily on randomized sham-procedure-controlled trials that were predominantly conducted on infantile and juvenile patients with SMA types 1 and 2 [6,7]. Adult patients of all SMA types were included to a lower extent in these clinical trials. Given the approval of nusinersen, future placebo- or sham-procedure-controlled trials in adult 5q-SMA are unlikely. Therefore, observational studies serve as an important, if not only, source of outcome research in adult 5q-SMA [8–12]. Recently registry studies demonstrated positive results of nusinersen treatment of adult 5q-SMA patients when applying clinical end-points that have been used in the infantile and juvenile populations before [11,13].

In adult 5q-SMA, the functional deficits and their perception may be highly variable and distinct from infantile and juvenile patients. Therefore, diverging expectations towards nusinersen and different perceptions of the therapy are assumed. Thus, this study aims to systematically investigate (i) demographic and clinical characteristics, (ii) individual treatment expectations, (iii) the subjective perception of outcome, (iv) treatment satisfaction and (v) the recommendation rate for the drug in adult 5q-SMA patients receiving nusinersen.

METHODS

Study design

An observational, longitudinal, multi-center study was conducted. The investigation was reported according to STROBE criteria [14].

Participants

Subjects meeting the following inclusion criteria were included in the cohort study: (i) genetically confirmed diagnosis of 5q-SMA, (ii) current or planned nusinersen treatment, (iii) age 18 years or older and (iv) informed consent for participation in the research platform APST [15–18].

Setting

The study was performed between July 2019 and September 2020 at nine specialized SMA treatment centers in Germany. SMA patients were enrolled in the observational study in two different settings:

recruitment before initiation of planned nusinersen therapy or during ongoing treatment (Figure S1).

Assessment and data capture

Assessment of clinical and demographic data was realized by issuing case report forms to be completed by neurologists, study coordinators and study assistants. Patient-reported outcomes were assessed using questionnaires in printed form or web-based structured interviews realized via the digital research platform APST [19].

Variables

Demographic and clinical data

The following demographic and clinical data were collected: gender, age at symptom onset, SMA type, disease duration, ventilation and nutrition support and Amyotrophic Lateral Sclerosis Functional Rating Scale—extended (ALS-FRS-ex, Table 1). ALS-FRS-ex is a validated instrument to assess motor functions of the bulbar region, the extremities and the trunk including breathing abilities and the requirement for ventilatory support. It comprises 15 items with five rating options (0 to 4). The total range of the scale spans 0 (poor function) to 60 scale points (full function) [20,21].

TABLE 1 Demographic data and clinical characteristics

Characteristics	Classification	Total cohort, n = 151	SMA type 1, n = 10	SMA type 2, n = 51	SMA type 3, n = 90
Gender	Male, % (n)	55.6 (85)	50.0 (5)	49.0 (25)	60.0 (54)
	Female, % (n)	44.4 (64)	50.0 (5)	51.0 (26)	40.0 (36)
SMA type	Type 1, % (n)	6.6 (10)	100 (10)	n/a	n/a
	Type 2, % (n)	33.8 (51)	n/a	100 (51)	n/a
	Type 3, % (n)	59.6 (90)	n/a	n/a	100 (90)
Age in years	At symptom onset, mean (SD; range)	5.30 (7.32; 0–42.17)	0.30 (0.27; 0–0.67)	1.35 (2.82; 0–19.25)	8.10 (8.12; 0–42.17)
	At therapy onset, mean (SD; range)	36.26 (13.30; 15.25–69.17)	28.17 (2.83; 15.25–39.50)	31.81 (1.79; 16.92–63.42)	39.85 (1.39; 17.0–69.17)
ALS-FRS-ex	Mean (SD; range)	40.1 (11.6; 3–59)	24.6 (3.2; 7–37)	32.7 (1.3; 3–56)	46.2 (0.9; 29–59)
Ventilation support	Total, % (n)	23.8 (36)	70.0 (7)	47.1 (24)	5.6 (5)
	NIV, % (n)	21.9 (33)	60.0 (6)	43.1 (22)	5.6 (5)
	TIV, % (n)	2.0 (3)	10.0 (1)	3.9 (2)	0 (0)
Nutrition support[a]	PEG, % (n)	6.0 (9)	40.0 (4)	9.8 (5)	0 (0)
Disease duration at therapy onset	Years, mean (SD; min–max)	30.8 (12.9; 1–63.1)	26.1 (11.6; 5.7–38.5)	17.8 (10.2; 0–38.8)	19.1 (10.9; 0–38.0)
Duration of nusinersen treatment in total	Months, mean (SD; min–max)	19.06 (10.81; 0–38.84)	26.10 (11.63; 5.65–38.51)	17.78 (10.21; 0–38.84)	19.07 (10.90; 0–38.02)
Duration of nusinersen treatment before first observation	Months, mean (SD; min–max)	6.13 (3.84, 0.46–16.04)	9.41 (3.55, 3.98–12.22)	6.37 (3.99, 0.95–14.26)	5.59 (3.63, 0.46–16.04)
Assessment interval of nusinersen therapy	Months, mean (SD; min–max)	6.1 (5.1; 0.5–16.0)	9.4 (3.6; 4.0–12.2)	6.4 (4.0; 1.0–14.3)	5.6 (3.6; 0.5–16.0)
Discontinuation of nusinersen therapy	Patient decision, % (n)	1.3 (2)	0 (0)	1.96 (1)	1.11 (1)
	Adverse events, % (n)	0 (0)	0 (0)	0 (0)	0 (0)
	Death, % (n)	0.7 (1)	0 (0)	1.96 (1)	0 (0)

Abbreviations: ALS-FRS-ex, Amyotrophic Lateral Sclerosis Functional Rating Scale—extended; n, number of patients; NIV, non-invasive ventilation; PEG, percutaneous endoscopic gastrostomy; TIV, tracheostomy with invasive ventilation.

[a]Supply of drinkable food was not recorded.

Nusinersen treatment

The following data were collected: age and disease duration at start of treatment, dates, intervals, circumstances (inpatient vs. outpatient) of treatment, administration of drug (manual lumbar puncture vs. fluoroscopy or computed tomography guided intrathecal administration) and discontinuation of therapy (timing and reasons).

Treatment expectations

Treatment expectations were assessed and weighted by the Measure Yourself Medical Outcome Profile (MYMOP2) [22–24]. The MYMOP is a brief, patient-generated, problem-specific questionnaire, which requires participants to qualify—and by that means prioritize—two symptoms or impairments that concern them most.

Perception of treatment

The perception of outcome was assessed by the MYMOP2 score. The nominal rating of the severity of symptoms on a seven-point Likert scale (0 for "as good as it could be" to 6 for "as bad as it could be") at different time points during the course of disease was used to quantitatively evaluate the perception of nusinersen.

Response to treatment

Patients showing an improvement in at least one of the two target symptoms—as assessed by MYMOP2—were defined as "responders" to nusinersen. Participants with reported improvement in one of the prioritized symptoms and deterioration of the other qualified symptom and patients with stable (unchanged) rating of at least one of the two prioritized symptoms were classified as "indifferent". Individuals reporting a deterioration in both target symptoms and their activity level were defined as "non-responders".

Treatment satisfaction

Satisfaction with nusinersen was assessed by means of the Treatment Satisfaction Questionnaire for Medication (TSQM-9). TSQM-9 is a validated questionnaire comprising nine questions concerning patients' satisfaction with medication [25–27]. The questions are answered on a five-point or seven-point scale (e.g., from very dissatisfied to very satisfied). Each of the nine questions is evaluated in a total score that can range from 0 to 100. A higher total score equates to greater satisfaction.

The total score is calculated as follows:

total score for question X

= [(response score of question X minus 1) ÷ (highest possible response score minus the lowest possible response score)] multiplied by 100

The questions referred to three dimensions: effectiveness (questions 1 to 3), convenience (questions 4 to 6) and global satisfaction (questions 7 to 9). The total scores for effectiveness, convenience and global satisfaction are calculated as follows:

1. total score for effectiveness: {[sum (response score for question 1 plus question 2 plus question 3) minus 3] divided by 18} multiplied by 100

2. total score for convenience: {[sum (response score for question 4 plus question 5 plus question 6) minus 3] divided by 18} multiplied by 100

3. total score for global satisfaction: {[sum (response score for question 7 plus question 8 plus question 9) minus 3] divided by 14} multiplied by 100

The TSQM-9 was analyzed for the total group and the following cohorts of treatment duration: (i) less than 12 months; (ii) 12 to 24 months; (iii) over 24 months.

Recommendation of treatment

The Net Promoter Score (NPS) was used for examining the patients' attitude towards their treatment with nusinersen [28]. This metric was calculated based on responses to a single question: "How likely is it that you would recommend nusinersen to a friend or colleague who suffers from SMA?" Possible answers ranged from 0 points (absolutely unlikely recommendation) to 10 points (highest likelihood of recommendation). Patients who responded with a score of 9–10 were considered as "promoters" (likely recommendation). Those who rated the medication with 7 or 8 were classified as "indifferent". The group of patients who responded with 6 to 0 points were defined as "detractors" (unlikely recommendation). The NPS was calculated by subtracting the percentage of detractors from the percentage of promoters. Indifferent patients counted toward the total number of respondents, thus decreasing the percentage of detractors and promoters. The NPS is calculated as follows: NPS = promoters (in percentage of all patients) minus detractors (in percentage of all patients). The NPS ranges between +100 and −100. Basically, a NPS with a positive score (>0) is regarded as a supporting recommendation; a result of +50 is considered excellent [28]. The NPS was analyzed for the total group and the following cohorts of treatment duration: (i) less or equal 12 months; (ii) 13 to 24 months; (iii) over 24 months.

Protocol approvals and registrations

The study protocol was approved by the Medical Ethics Committee of the Charité—Universitätsmedizin Berlin, Germany, under the number EA1/219/15. A signed patient information and informed consent form was obtained from all participants.

Statistical methods

Descriptive analyses were performed to compare frequencies within the parameters assessed. Significant differences between the parameters and, respectively, subgroups of nominally scaled data were assessed by contingency tables and the chi-squared test. The Wilcoxon test was employed for the analysis of the statistical power of ordinally scaled data, whilst metric data were subjected to the *t* test (MYMOP, ALS-FRS-ex). Statistical significance was ascertained according to an error risk of up to 5% (*p* value <0.05). Statistical effect size of mean differences was classified as follows: small effect size: $d \geq 0.2$, medium effect size: $d \geq 0.5$, and large effect size: $d \geq 0.8$. For significance analysis, each pair of variables was considered for which data were available (pairwise deletion). Data analysis was based on SPSS (version 25.0).

RESULTS

Sample characteristics

In total, 151 patients at nine specialized SMA centers were included in the observational study (Figure S2). 15.2% of the patients (*n* = 23) were recruited before initiation of planned nusinersen therapy and 84.8% (*n* = 128) during ongoing nusinersen maintenance treatment (Figure S1).

### Demographic data and clinical characteristics

A summary of demographic and clinical data is given in Table 1 and provided for the total cohort as well as for SMA types 1–3.

Nusinersen treatment

A summary of data on nusinersen therapy is given in Table 1 and provided for the total cohort as well as for SMA types 1–3.

Treatment expectations

The results are shown in Figure 1 and Table S1. Using MYMOP2, treatment expectations of 151 patients and 296 prioritized symptoms were captured. In general, strong differences in the ranking of target symptoms were found between SMA types 1 to 3. In SMA types 1 and 2, symptoms (and functional impairment) in the upper extremities were most frequently prioritized. In contrast, in SMA type 3 most of the expectations concerned leg functions. Strikingly, amongst patients with SMA types 1 and 2 there were no (SMA type 1) or few (SMA type 2) expectations for symptomatic or functional improvement of the lower extremities although ambulation and other leg functions are severely affected in these SMA types.
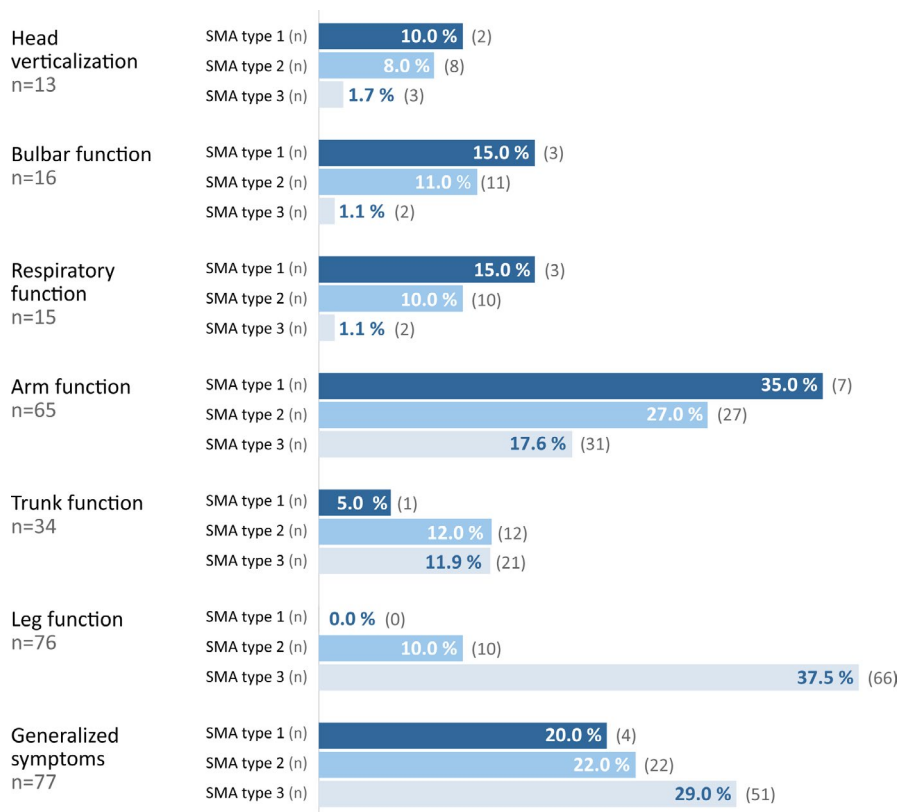
FIGURE 1 Treatment expectations in terms of prioritized symptoms as assessed by the MYMOP2 scale. MYMOP, Measure Yourself Medical Outcome Profile; *n*, number of patients [Colour figure can be viewed at wileyonlinelibrary.com]

Respiratory and bulbar functions as well as head verticalization were mainly prioritized in SMA types 1 and 2. However, expectations to improve trunk functions were predominantly reported in SMA type 3. Generalized symptoms such as pain, contractures and weakness made up 26% (*n* = 77) of the treatment expectations (Table S1).

Perception of treatment

The results are shown in Figure 2 and Table 2. At basic assessment (Figure S1), the mean symptom severity as assessed on the MYMOP2 seven-point Likert scale was 3.7 (*n* = 178). During follow-up of nusinersen therapy, a reduced symptom severity of 3.3 scale points was identified (10% relative decline in symptom severity, *p* < 0.001). In particular, a marked improvement was noted for head verticalization (ability to keep the head up and stabilize it) and also for speech and swallowing function (reduction by 1.3 scale points; 37% relative reduction; *p* < 0.004). In respiratory functions, there was no change in symptom severity. Beyond prioritized symptoms, 51% of patients (*n* = 45) perceived an increase in their level of activity over the course of nusinersen therapy (*p* < 0.001).

Response to treatment

Of all 5q-SMA patients, 64% (*n* = 59) perceived an improvement in at least one of the two target symptoms, being by definition "responders"

to nusinersen therapy. Of all responders, 26% (*n* = 24) reported an improvement in both prioritized symptoms. 14% of patients (*n* = 13) were allocated to the "indifferent" group. Only one patient (1.1%) perceived deterioration in both target symptoms and was classified as "non-responder".

Treatment satisfaction

The patients' treatment satisfaction with nusinersen, as assessed by TSQM-9, is shown in Figure 3 and Figure S3. The question "how confident are you that taking this medication is a good thing for you?" received the highest score of all the nine TSQM-related questions, followed by the question concerning the "overall satisfaction". Furthermore, treatment satisfaction was rated positively in relation to the duration of nusinersen therapy. In contrast, the questions about the usability and convenience of the drug were rated critical. The questions about convenience were the only ones to show no increase in satisfaction.

Recommendation of treatment

In total, 63.3% patients (*n* = 89) were promoters of nusinersen. Overall, the share of detractors was low (12.8%, *n* = 18). The NPS total score—the difference between promoters and detractors—was +51 (Figure 4). In fact, NPS values greater than 0 are classified as a positive rating whereas an NPS total score of > 50 is considered
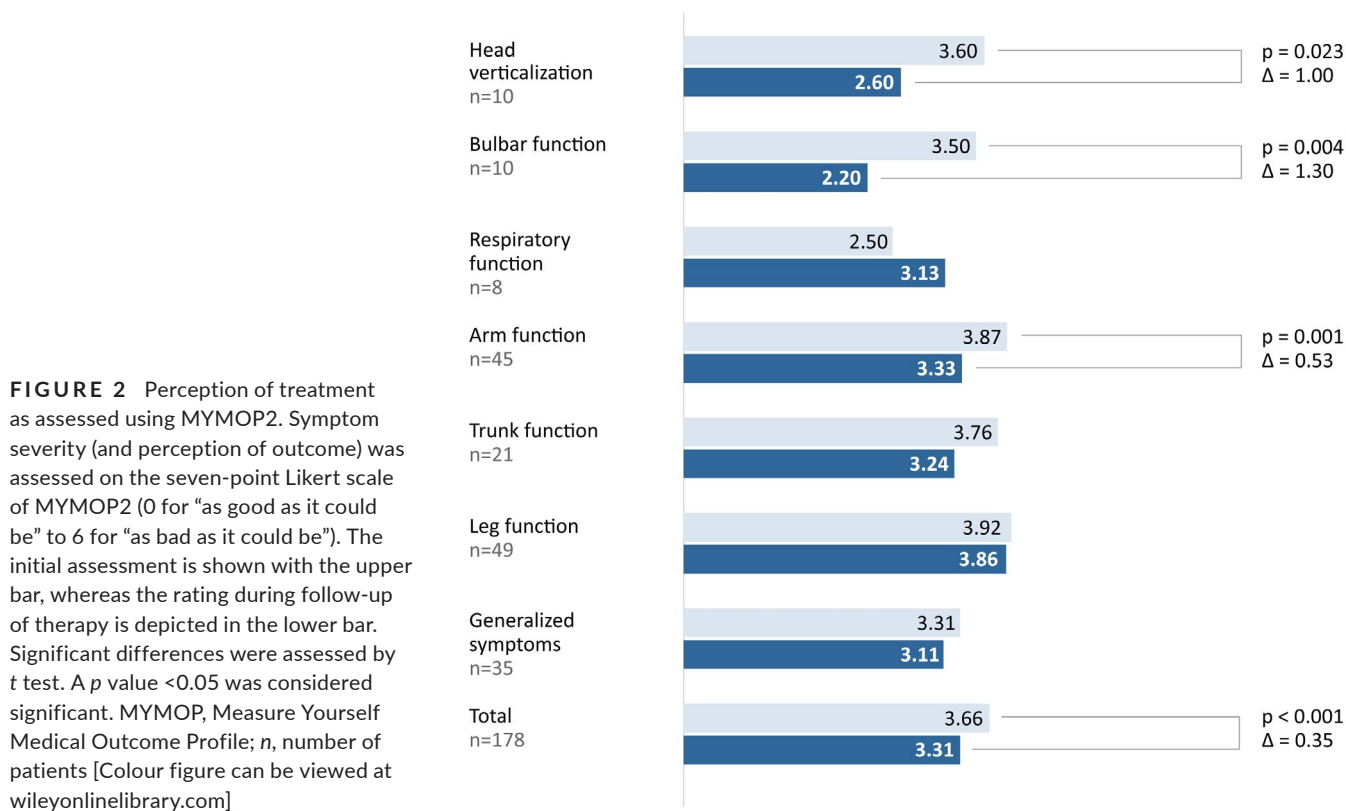
FIGURE 2 Perception of treatment as assessed using MYMOP2. Symptom severity (and perception of outcome) was assessed on the seven-point Likert scale of MYMOP2 (0 for "as good as it could be" to 6 for "as bad as it could be"). The initial assessment is shown with the upper bar, whereas the rating during follow-up of therapy is depicted in the lower bar. Significant differences were assessed by *t* test. A *p* value <0.05 was considered significant. MYMOP, Measure Yourself Medical Outcome Profile; *n*, number of patients [Colour figure can be viewed at wileyonlinelibrary.com]

Head verticalization n=10: 3.60 / 2.60 — p = 0.023, Δ = 1.00
Bulbar function n=10: 3.50 / 2.20 — p = 0.004, Δ = 1.30
Respiratory function n=8: 2.50 / 3.13
Arm function n=45: 3.87 / 3.33 — p = 0.001, Δ = 0.53
Trunk function n=21: 3.76 / 3.24
Leg function n=49: 3.92 / 3.86
Generalized symptoms n=35: 3.31 / 3.11
Total n=178: 3.66 / 3.31 — p < 0.001, Δ = 0.35

TABLE 2 Expectations of treatment and perception of therapy as assessed by MYMOP2

Target symptom	Number of patients, % (n)	Basic survey, mean (SD)	Final survey, mean (SD)	M difference (SD; 95% CI)	p value[b]	d[c]	Observation interval[d], mean (SD)	Responsiveness, number of patients, % (n)			Therapy duration[d], mean (SD)
								R	I	Non-R	
Head verticalization	10.9 (10)	3.60 (1.6)	2.60 (1.3)	1.00 (1.16; 0.17–1.83)	0.023	0.87	8.8 (3.9)	70.0 (7)	20.0 (2)	10.0 (1)	16.7 (9.6)
Bulbar function[a]	10.9 (10)	3.50 (1.2)	2.20 (1.8)	1.30 (1.06; 0.54–2.06)	0.004	1.23	4.4 (3.1)	90.0 (9)	0 (0)	10.0 (0)	14.6 (12.2)
Speaking	–	–	–		–	–	–	–	–	–	–
Swallowing	7.6 (7)	3.57 (0.8)	2.43 (1.7)	1.14 (1.07; 0.15–2.13)	0.03	1.07	5.0 (3.5)	85.7 (6)	0 (0)	14.3 (1)	17.0 (12.4)
Chewing	3.3 (3)	3.33 (2.1)	1.67 (2.1)	1.67 (1.16; –1.2–4.54)	0.13	1.44	3.2 (1.9)	100 (3)	0 (0)	0 (0)	8.9 (11.7)
Respiratory function	8.7 (8)	2.50 (0.9)	3.13 (1.1)	–0.63 (1.60; –1.96–0.71)	0.305	0.39	4.5 (2.6)	12.5 (1)	50.0 (4)	37.5 (3)	14.2 (12.1)
Arm function[a]	42.4 (39)	3.87 (1.2)	3.33 (1.2)	0.53 (0.99; 0.24–0.83)	0.001	0.54	6.6 (4.1)	53.8 (21)	38.5 (15)	7.7 (3)	16.9 (9.5)
Arm function close to body	26.1 (24)	3.83 (1.1)	3.38 (1.2)	0.46 (1.10; –0.01–0.92)	0.053	0.42	6.0 (4.5)	54.2 (13)	33.3 (8)	12.5 (3)	16.7 (9.9)
Hand function	22.8 (21)	3.90 (1.3)	3.29 (1.2)	0.62 (0.87; 0.23–1.01)	0.004	0.716	7.1 (3.6)	57.1 (12)	33.3 (7)	9.5 (2)	17.1 (9.2)
Trunk function[a]	22.8 (21)	3.76 (1.4)	3.24 (1.7)	0.52 (1.69; –0.25–1.29)	0.171	0.31	7.2 (3.9)	52.4 (11)	33.3 (7)	14.3 (3)	21.2 (7.1)
Stability of trunk	16.3 (15)	3.87 (1.1)	2.93 (1.5)	0.93 (1.67; 0.1–1.86)	0.048	0.56	6.9 (4.1)	66.7 (10)	26.7 (4)	6.7 (1)	22.9 (6.4)
Sitting	5.4 (5)	3.60 (2.3)	4.40 (2.1)	–0.80 (1.30; –2.42–0.82)	0.242	0.61	8.5 (3.9)	0 (0)	60.0 (3)	40.0 (2)	17.2 (8.2)
Coughing	1.1 (1)	3.0 (–)	2.0 (–)		–	–	5.2 (–)	100 (1)	0 (0)	0 (0)	15.3 (–)
Leg function[a]	43.9 (40)	3.92 (1.1)	3.86 (1.3)	0.06 (1.07; –0.25–0.37)	0.69	0.06	4.2 (3.1)	37.5 (14)	47.5 (19)	17.5 (7)	14.7 (10.6)
Leg strength	26.1 (24)	4.04 (1.1)	3.54 (1.1)	0.50 (0.93; 0.11–0.89)	0.015	0.54	4.5 (3.5)	45.8 (11)	50.0 (12)	4.2 (1)	14.3 (10.9)
Walking	13.0 (12)	4.17 (1.0)	4.67 (0.89)	–0.50 (0.91; –1.07–0.07)	0.082	0.55	4.0 (3.0)	8.3 (1)	50.0 (6)	41.7 (5)	16.0 (10.6)
Standing	3.3 (3)	4.00 (1.7)	4.67 (2.3)	–0.67 (2.08; –5.84–4.50)	0.635	0.32	4.7 (4.4)	33.3 (1)	33.3 (1)	33.3 (1)	19.1 (9.3)

(Continues)

TABLE 2 (Continued)

Target symptom	Number of patients, % (n)	Basic survey, mean (SD)	Final survey, mean (SD)	M difference (SD; 95% CI)	p value[b]	d[c]	Observation interval[d], mean (SD)	Responsiveness, number of patients, % (n)			Therapy duration[d], mean (SD)
								R	I	Non-R	
Climbing stairs	*10.9 (10)*	*3.30 (1.2)*	*3.40 (1.2)*	*−0.10 (0.88; −0.73–0.53)*	*0.726*	*0.11*	*3.5 (1.9)*	*20.0 (2)*	*60.0 (6)*	*20.0 (2)*	*12.8 (11.5)*
Globalized symptoms[a]	**31.5 (29)**	**3.31 (1.2)**	**3.11 (1.4)**	**0.20 (1,45; −0.30–0.70)**	**0.421**	**0.14**	**6.9 (3.7)**	**48.3 (14)**	**27.6 (8)**	**24.1 (7)**	**22.1 (9.1)**
Generalized weakness	*22.8 (21)*	*3.23 (1.3)*	*3.00 (1.7)*	*0.23 (1.5; −0.44–0.90)*	*0.488*	*0.15*	*6.4 (3.6)*	*47.6 (10)*	*23.8 (5)*	*28.6 (6)*	*23.1 (9.6)*
Pain	*8.7 (8)*	*3.88 (1.1)*	*3.63 (0.7)*	*0.25 (1.67; −1.14–1.64)*	*0.685*	*0.15*	*8.0 (4.5)*	*37.5 (3)*	*25.0 (2)*	*37.5 (3)*	*19.1 (9.7)*
Contractures	*1.1 (1)*	*4.00 (-)*	*3.00 (-)*	*-*	*-*	*-*	*11.9 (-)*	*100 (1)*	*0 (0)*	*0 (0)*	*14.0 (-)*
Tremor	*-*	*-*	*-*	*-*	*-*	*-*	*-*	*-*	*-*	*-*	*-*
Motor restlessness	*1.1 (1)*	*2.00 (-)*	*2.00 (-)*	*-*	*-*	*-*	*8.0 (-)*	*0 (0)*	*100 (1)*	*0 (0)*	*21.7 (-)*
Muscle cramps	*-*	*-*	*-*	*-*	*-*	*-*	*-*	*-*	*-*	*-*	*-*
Feeling cold/shivery	*1.1 (1)*	*2.00 (-)*	*3.00 (-)*	*-*	*-*	*-*	*6.0 (-)*	*0 (0)*	*0 (0)*	*100 (1)*	*27.7 (-)*
Orthostatic response	*11.1 (1)*	*3.00 (-)*	*2.00 (-)*	*-*	*-*	*-*	*5.4 (-)*	*100 (1)*	*0 (0)*	*0 (0)*	*31.1 (-)*
Total symptoms	**100 (92)**	**3.66 (1.3)**	**3.31 (1.4)**	**0.35 (1.29; 0.16–0.54)**	**<0.001**	**0.27**	**6.0 (3.8)**	**64.1 (59)**	**30.4 (28)**	**5.4 (5)**	**17.6 (10.1)**
Activity	**88**	**4.18 (1.5)**	**3.55 (1.6)**	**0.64 (1.50; 0.32–0.96)**	**<0.001**	**0.42**	**6.1 (3.9)**	**51.1 (45)**	**30.7 (27)**	**18.2 (16)**	**17.3 (1.6)**

Note:: Target symptoms were assessed by the MYMOP2, which requires participants to qualify two symptoms or impairments that concern them most (italic), and categorized accordingly (bold). Weighting of symptoms using the Likert scale (6, as bad as it gets; 0, as good as it gets). The rating of symptom severity was performed at an initial assessment (basic survey) and during follow-up of nusinersen therapy (final survey).

Abbreviations: CI, confidence interval; *d*, Cohen's *d*, effect size; I, indifferent; MYMOP, Measure Yourself Medical Outcome Profile; *n*, number of patients; Non-R, non-responder; R, responder.

[a]Cumulative.

[b]Mean differences were accessed by *t* test. A *p* value < 0.05 was considered as statistically significant.

[c]Statistical effect size of mean differences was classified as follows: small effect size: *d* ≥ 0.2, medium effect size: *d* ≥ 0.5, and large effect size: *d* ≥ 0.8 [33].

[d]In months.

excellent [14]. Remarkably, patients with SMA types 1 and 2 submitted stronger recommendations (NPS +66.7 and +65.3, respectively) compared to patients with SMA type 3 (NPS +40.2). The overall positive results were supported by the greatest number of promoters in the group of SMA patients with a long treatment period (> 12 months) compared to shorter therapy (Figure 4).

DISCUSSION

Sample selection, demographic and clinical characteristics

In this study, a systematic assessment of nusinersen therapy in a real-world setting was realized. However, the study was confined to specialized SMA centers. Therefore, the possibility that patients may not be representative of those seen outside this setting cannot be excluded. Thus, it is conceivable that 5q-SMA patients with higher age and longer disease duration may be overrepresented.

The median age at the start of therapy was 36 years. Remarkably, the highest age at treatment onset was 69 years. Obviously, there was no age threshold on nusinersen treatment. SMA type 3 (60%) was the predominant type in the cohort. These findings were in correspondence to previous reports [10,11,13]. The smaller share of SMA type 1 (7%) and 2 (34%) may reflect the lower prevalence of both types in the adult 5q-SMA population. Furthermore, a more reserved attitude towards taking up therapy cannot be excluded although these psychosocial and behavioral aspects were not investigated in this study. The functional deficit as assessed by the ALS-FRS-ex was severe in most patients (mean 40.1), but showed a wide range of functional impairment. However, the ALS-FRS-ex scale has not been applied to SMA patients. Thus, the use of this score is considered exploratory and needs to be confirmed by other studies and investigators. Despite the methodological limitations of this score, patients with severe functional deficits (13.5% of patients with ALS-FRS-ex < 30), invasive nutrition intervention (6% of patients with percutaneous endoscopic gastrostomy) or ventilation support (23.8% of patients with non-invasive ventilation or tracheostomy with invasive ventilation) contributed to the notion that there was no distinct deficit threshold preventing patients from nusinersen therapy (likewise the "unlimited" age at the start of treatment). Conversely, the wide spectrum of disease severity may explain the diversity of treatment expectations as documented by MYMOP2.

Treatment expectation and perception of nusinersen therapy

The result of the MYMOP2 survey showed a broad spectrum of treatment goals. The definition of treatment expectations such as the functional deficits, psychosocial values, social resources and participation options varied substantially amongst individuals. Patients with SMA types 1 and 2 typically presented with high-grade paresis of the legs, which, however, was not amongst the prioritized symptoms. Thus, the results of MYMOP2 were indicative of a possible discrepancy between functional deficit and treatment expectations whereas the most severe functional deficits were not necessarily prioritized as target symptoms. This discrepancy may be discussed from two angles: (i) patients have no real expectations as to the improvement to be gained with therapy or (ii) the subjective burden perceived with this deficit is given less priority compared with other symptoms. However, the clarification of this unsolved question was not pursued in this study and will be the subject of future investigations.

In this study, the Revised Upper Limb Module (RULM) or Hammersmith Functional Motor Scale Expanded (HFMSE) were not investigated, although these scales are commonly used in randomized trials and observational studies [11,13]. The reason for refraining from using the RULM and HFMSE was the focus on the perception of nusinersen therapy and the assessment of symptoms that were not covered by RULM and HFMSE (such as bulbar and respiratory symptoms). Notwithstanding, in future studies an assessment of established clinical end-points in combination with patient-reported outcomes (e.g., MYMOP) is of interest. MYMOP2 allowed for monitoring of the patient-reported outcome over the course of therapy. The observation covered the complete range of prioritized symptoms including the perception of speech, swallowing and mobility. During nusinersen treatment, symptom severity decreased by 10% ($p < 0.001$). The scale of these changes corresponded to improvements reported in other observational studies using RULM, HFMSE and the 6-min walk test [11,13]. In this investigation, a significant improvement was perceived for head verticalization (28% decrease of MYMOP2 symptom severity, $p < 0.023$) and bulbar functions (37%, $p < 0.004$), two domains that were not covered in the RULM and HFMSE instruments. The prioritization of respiratory functions was rather low (11% of SMA types 1 and 2 patients). This corresponds with the low rate of non-invasive

FIGURE 3 Treatment satisfaction with nusinersen, as assessed by the Treatment Satisfaction Questionnaire for Medication (TSQM-9). The score was evaluated separately in nine questions as follows. (a) Question 1— the ability of nusinersen to treat or prevent SMA: "How satisfied or dissatisfied are you with the ability of nusinersen to prevent or treat SMA?" (b) Question 2—the way nusinersen relieves symptoms of SMA: "How satisfied or dissatisfied are you with the way nusinersen relieves your symptoms?" (c) Question 3—the amount of time it takes nusinersen to start working: "How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?" (d) Question 4—the usability of nusinersen: "How easy or difficult is it to use the medication in its current form?" (e) Question 5—planning when to use nusinersen: "How easy or difficult is it to plan when you will use the medication each time?" (f) Question 6—administration of nusinersen as instructed: "How convenient or inconvenient is it to take the medication as instructed?" (g) Question 7—taking nusinersen is a good thing: "Overall, how confident are you that taking this medication is a good thing for you?" (h) Question 8—the good things about nusinersen outweigh the bad things: "How satisfied are you that the good things about this medication outweigh the bad things?" (i) Question 9—overall satisfaction with nusinersen: "Taking all things into account, how satisfied or dissatisfied are you with this medication?" *n*, number of patients [Colour figure can be viewed at wileyonlinelibrary.com]
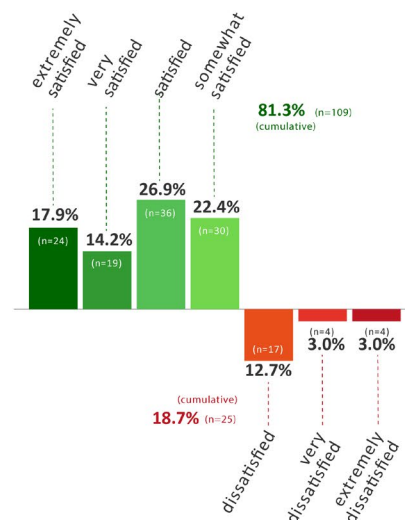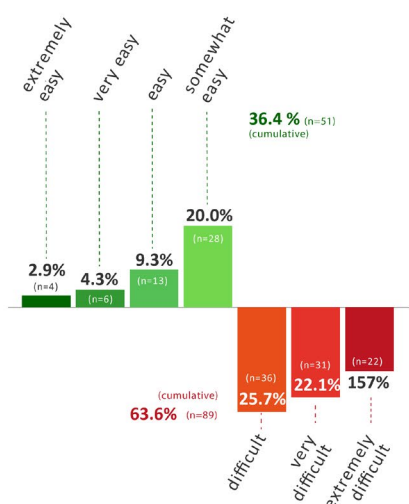
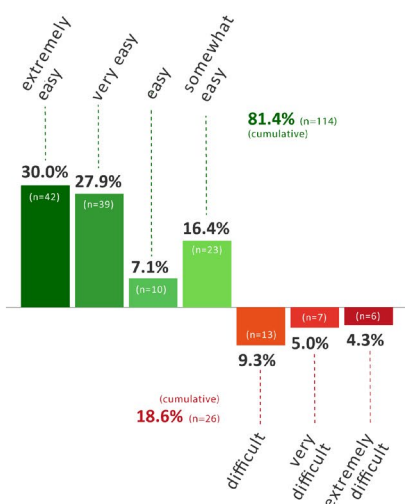**(a)** Treatment or prevention
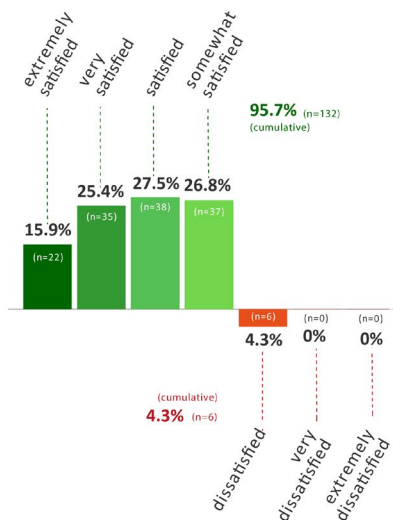
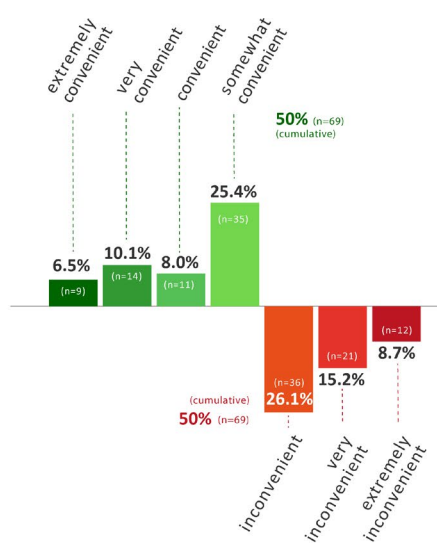**(b)** Symptom relief
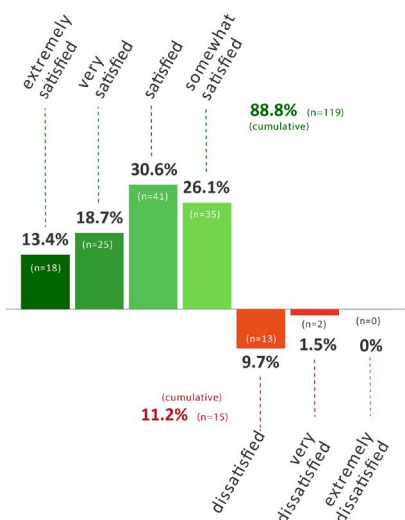
(c) Speed of action
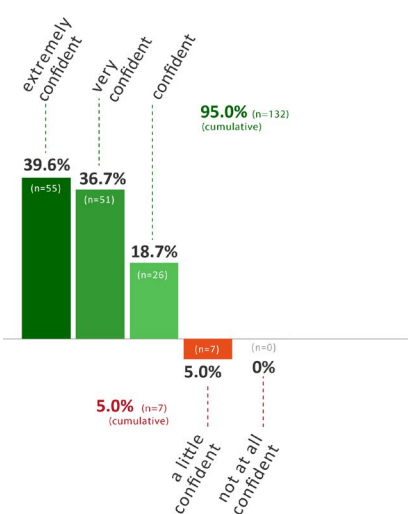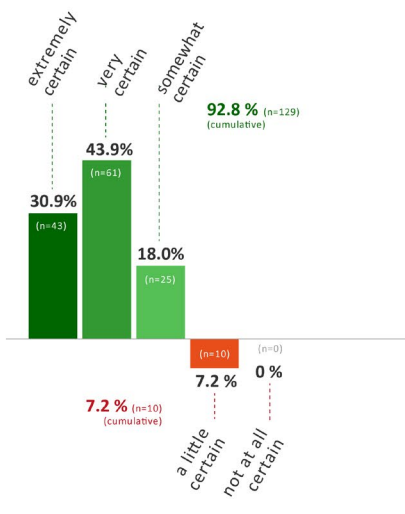
(d) Ease of use
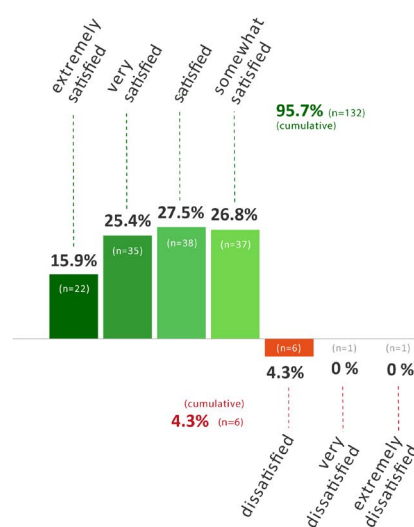
(e) Ease of planning

(f) Ease of using as instructed

(g) Confidence in drug

(h) Confidence in advantage of drug

(i) Global satisfaction

(a)

■ Likely recommendation   ■ Indifferent recommendation   ■ Unlikely recommendation

≤ 12 months treatment
(n=38)

13 to 24 months treatment
(n=47)

> 24 months treatment
(n=55)

(b)

FIGURE 4 Recommendation of nusinersen using the Net Promoter Score (NPS) relative to the duration of therapy. The NPS was applied to assess the patients' likelihood to recommend this drug. This metric was calculated based on responses to a single question: "How likely is it that you would recommend nusinersen to a friend or colleague who suffers from SMA?" The answers were rated between 0 points (absolutely unlikely recommendation) and 10 points (highest likelihood of recommendation). Patients who responded with a score of 9 to 10 were considered as "promoters". Those who rated the medication with 7 or 8 were classified as "indifferent". The patients who responded with 6 to 0 points were defined as "detractors". The NPS is calculated by subtracting the percentage of patients who are detractors from the percentage of patients who are promoters. *n*, number of patients [Colour figure can be viewed at wileyonlinelibrary.com]

ventilation in the studied cohort (21.9%, *n* = 33), which is well in line with other reports on the rate of non-invasive ventilation in SMA [29]. A methodological limitation of the study is the confinement to subjective outcome measures. Thus, improved mobility was measured in terms of subjective perception on the MYMOP2 Likert scale and was not objectified by functional parameters. Nevertheless, it may well be conceivable that the improved motor function in arms and hands may translate into improved handling of walkers (upper and lower extremities) and wheelchairs (e.g., hand function for using joysticks); and that means that, even in

wheelchair-using patients, improved mobility may be reached and perceived. However, in further studies an objectification of functional improvements is desirable and of importance.

By definition, patients were classified as "responders", "indifferent" or "non-responders" based on the MYMOP2 score in the course of nusinersen therapy. The response criteria were defined for the purpose of this study and have not yet been validated by comparative studies. The term "responder" is thus limited to the subjective perception of symptom severity and may not reflect "objective" clinical end-points such as RULM or HFMSE. 64% of patients (*n* = 59)

were "responders", a finding that corresponds to the response rate of 69% in a reported observational study in which HFMSE was used as the outcome parameter [11]. A major methodological limitation concerning the classification of responders is caused by the timing of assessment in relation to beginning of treatment and recruitment to this observational study. Most of the patients (85%) were recruited to the study during ongoing nusinersen treatment. Therefore, a comparison of symptom severity before and after nusinersen therapy was not possible. Despite this limitation, the responder concept was applied as the Likert scale of MYMOP2 allowed the quantification of symptom severity during the further course of treatment.

Treatment satisfaction and recommendation

On the TSQM-9 score, 68.8% of patients gave a positive rating ("extremely satisfied" to "satisfied") in the summarizing question on global satisfaction. This percentage of patients was of the order of "responders" and by that means corresponds to the findings of the MYMOP2 score. In contrast to the positive ratings for efficacy and global satisfaction, the domain of convenience was rated more critically. Although the reasons for the patients' dissatisfaction were not assessed, the lumbar puncture for intrathecal administration and the inpatient setting of nusinersen therapy in most cases might be at the basis of the critical view on the convenience of treatment. The present data may support the exploration of alternative methods of administration (such as intrathecal pumps) [27]. However, despite the burden (e.g., lumbar puncture) and efforts (hospital admission) associated with the therapy, the discontinuation of nusinersen treatment was a rare event (2%).

The NPS serves as a robust instrument for the assessment of products and services [28]. Although the validation of this score in medicine is still limited, the NPS finds growing use in outcome research, mainly due to the simplicity of the method and the established calculation matrix [30–32]. In this study, the NPS score for nusinersen was +66 which translates into a very positive recommendation rate. Furthermore, the fact that the NPS was higher the longer patients were under therapy underpinned the positive recommendation rate. In fact, in market research NPS results >50 are considered "excellent". However, there is limited experience with this score in the medical setting and caution is warranted when transferring the NPS system of validating products and services to treatment options.

The positive NPS and TSQM-9 results were surprising as this cohort presented with severe deficits and only slight improvements over the treatment course. This observation gives rise to the premise that high treatment satisfaction can be gained with moderate or slight functional improvement. It touches upon the measurability of minimal functional effects and their meaningfulness for mobility, communication and social inclusion of SMA patients. However, the psychosocial dimension of outcomes was beyond the scope of this study and needs further research.

In summary, nusinersen therapy in adult 5q-SMA patients was used in a wide spectrum of patients in terms of age, duration of disease and functional deficits. The treatment expectations towards nusinersen were highly variable and referred to the severity of disease and the pattern of symptoms and impairments. The majority of patients experienced an alleviation of symptoms and motor deficits, rated as small or moderate. Despite the rather slight degree of perceived functional improvements, the treatment satisfaction was high and recommendation rates were excellent. In future studies, the patient-reported outcomes over the course of longer treatment periods and the correlation to functional parameters are of major interest.

CONFLICT OF INTEREST

TM and CM are founders of the digital management and research platform APST and hold shares in Ambulanzpartner Soziotechnologie APST GmbH.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.